DECLARATION OF DR. TOMASZ HEYDUK UNDER 37 C.F.R. §1.132

I, Tomasz Heyduk, declare and state as follows:

1. I have over 18 years of experience in the field of chemistry and biochemistry. I am currently employed as a professor for St. Louis University, and have worked at St. Louis University since 1992. My educational background includes a Bachelor of Science degree in the chemical sciences awarded by the University of Wroclaw in the year 1979 and a doctorate degree (i.e., PhD) in Chemistry awarded by the Technical University in the year 1986. I have also published over 65 scientific papers and presented numerous abstracts at internationally attended meetings. Attached to this declaration is a copy of my curricula vitae.

2. I am a co-inventor of U.S. Patent Application Serial No. 10/539,107 ('107 application) entitled "Biosensors for Detecting Macromolecules and Other Analytes." In light of my first hand knowledge of the '107 application and my knowledge of the state of the art at the time of the filing of the application, I state the following:

3. For a given nucleic acid duplex, the free energy depends on three factors: the temperature, the salt concentration, and the nucleotide composition of the duplex.

    a. Claim 109 of the '107 application defines two of these three conditions: temperature and salt concentration.
        i. The temperature must be from about 21°C to about 40°C.
        ii. The salt concentration must be from about 1mM to about 100mM.
    b. The third condition (i.e. the nucleotide composition of the duplex), would be (a) either known in a given situation, or (b) able to be determined using common sequencing technology.
    c. Based on these three parameters, one of skill in the art would be able to experimentally calculate the free energy of a nucleic acid duplex.

i. This would allow one of skill in the art to determine if a known nucleic acid duplex falls within the claimed range of about 5.5 kcal/mol to 8.0 kcal/mole.

d. Generally speaking, there are two steps to calculating free energy experimentally.
   i. First, the melting curve of a nucleic acid duplex is generated. The melting curve is the relationship of the dissociation of a nucleic acid duplex as a function of temperature.
   ii. Second, the free energy is determined mathematically from the melting curve data.
   iii. Both steps are well known in the art. By way of example, please see SantaLucia et al., Biochemistry (1996) 35:3555-62.

4. The experimental method outlined above has been used to develop "nearest neighbor" free energy parameters that can be useful tools to ***predict*** free energy without having to perform the experiment. These parameters, however, are only predictions.
   a. "Nearest neighbor" parameters are based on the premise that the free energy of a given complementary base pair is based on the context of that base pair in the surrounding nucleic acid sequence, i.e., the neighbor.
   b. *Depending on experimental conditions*, these parameters may vary, as evidenced by Table 1 of SantaLucia, PNAS (1998) 95:1460-65.
      i. These variations do not necessarily stem from different ***methods*** of calculating free energy, but rather, from the experimental conditions, as summarized in Table 1, and/or the method used to extrapolate the nearest neighbor parameters from the calculated free energy values. These variations resulted in the different nearest neighbor parameters listed in Table 1 of the SantaLucia PNAS paper.
   c. As a result, a given set of nearest neighbor parameters are typically applicable only for the conditions used to develop the parameters, and must be further modified using mathematical estimations to account for different temperature or salt concentrations.
   d. **Consequently, the most direct way of determining free energy is experimentally, as opposed to relying solely on extrapolated "nearest neighbor" predictions.**

5. I further declare that all statements made herein of my own knowledge are true and that all statements made on information

and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

T. Heyduk
Tomasz Heyduk

05-18-10
Date

CURRICULUM VITAE

NAME:Tomasz Heyduk

HOME ADDRESS: 2510 Johnson Place Dr., Ballwin, MO 63021

BIRTH DATE: December 29, 1956

EDUCATION:

Institution	Date	Major	Degree
University of Wroclaw Wroclaw, Poland	1979	Chemical Sciences	M.Sc.
Technical University of Wroclaw Wroclaw, Poland	1986	Chemistry	Ph.D.

CURRENT POSITION AND ADDRESS:

Professor
Department of Biochemistry and Molecular Biology
St. Louis University School of Medicine
1402 South Grand Boulevard
St. Louis, MO 63104

PREVIOUS PROFESSIONAL EXPERIENCE:

1980-1986	Graduate Student and Teaching Assistant, Technical University of Wroclaw, Poland.
1986-1987	Research Associate, Technical University of Wroclaw, Poland.
1987-1989	Postdoctoral Fellow, St. Louis University School of Medicine, Department of Biochemistry and Molecular Biology, St. Louis, MO.
1989-1991	Research Assistant Professor, Dept. of Biochemistry and Molecular Biology, St. Louis University School of Medicine, St. Louis, MO..
1991-1992	Research Assistant Professor, The University of Texas, Medical Branch, Galveston, TX.
1992-1998	Assistant Professor, Dept. of Biochemistry and Molecular Biology, St. Louis University School of Medicine, St. Louis, MO.
1998-2003	Associate Professor, Dept. of Biochemistry and Molecular Biology, St. Louis University School of Medicine, St. Louis, MO.
2003-present	Professor, Dept. of Biochemistry and Molecular Biology, St. Louis University School of Medicine, St. Louis, MO.
2007-present	Associate Director for Basic Science, Saint Louis University Cancer Center

PROFESSIONAL SOCIETY MEMBERSHIPS:

Biophysical Society, ASMB

HONORARY SOCIETIES, HONORS AND AWARDS:

Polish Ministry of Higher Education. Outstanding Ph.D. dissertation in 1986
Outstanding Faculty/Mentor (Graduate Student Association), 1996

PROFESSIONAL SERVICES:

Ad hoc reviewer for:

Analytical Chemistry
Analytical Biochemistry
Biochemistry
Biophysical Chemistry
Biophysical Journal
Bioconjugate Chemistry
BioTechniques
Combinatorial Chemistry and High Throughput Screening
Chem Biochem
Journal of American Chemical Society
Journal of Biological Chemistry
Journal of Molecular Biology
Journal of Fluorescence
Molecular and Cellular Biology
Nature Methods
Nature Structural and Molecular Biology
Nature

Gibbs Conference, co-organizer (1991)
Gibbs Conference, treasurer (1992-2001)
Ad hoc reviewer for NSF grant applications
Ad hoc member of American Cancer Society Advisory Committee on Personnel for Research - A (1994)
Ad hoc member of NIH NIAID Special Emphasis Panel "Innovation Grant Program for Approaches in HIV Vaccine Research" (June 1998).
Ad hoc member of NIH BBCA study section, June 1999.
NIH Special Emphasis Panel and Project Site Visit to the Fluorescence Dynamics Resource, Urbana, IL (2000)
Permanent member of NIH BBCA study section (October 2002 - October 2004).
Permanent member of NIH MSFC study section (February 2004 - October 2007).

RESEARCH SUPPORT:

<u>Ongoing Research Support</u>

RO1 GM 50514 Heyduk (PI) 08/01/03-07/31/09
No cost extension
NIH/NIGMS
Inter and intramolecular communications in transcription.
The major goal of this project is to understand the role of s^{70} subunit of RNA polymerase in transcription initiation.
Role: PI

R41HG003964 Heyduk (PI) 09/19/06-08/31/09
No cost extension
NIH/NHGRI
Microarrays for DNA binding proteins
The goal of this project is to develop highly multiplexed microarrays for detecting sequence-specific DNA binding proteins.
Role:PI

AHA Heyduk(PI) 01/01/07-12/31/08
Enhanced affinity bivalent ligands and inhibitors
The major goal of this project is to develop bivalent enhanced affinity ligands for thrombin.
Role: PI

R41 GM079891 Heyduk (PI) 03/01/2007-02/28/2009
No cost extension
NIH/NIGMS
Rapid homogeneous antibody-based detection of proteins
The major goal of this project is to develop antibody-based homogenous molecular pincer assay for detecting proteins.
Role: PI

JDRF Heyduk (PI) 04/01/2007 – 3/31/2009
No cost extension
New methodologies for real time assessment of beta-cell function
The major goal of this proposal is to develop new assay for rapid determination of insulin and C-peptide
Role: PI

Pending

R42 GM079891 Heyduk (PI) 07/01/2008-06/30/2010
NIH/GM
Rapid homogeneous antibody-based detection of proteins
The major goal of this project is to develop antibody-based homogenous molecular pincer assay for detecting proteins. This is Phase II STTR proposal.
Role: PI

R41 AI081381 Heyduk, T. (PI) 11/01/2008-10/30/2010
Title: Rapid sensing of pathogenic bacteria
Project goals: The goal of this project will to develop sensors for rapid detection of pathogenic bacteria and viruses.
Role: PI

R21 CA137705 Heyduk, T. (PI) 09/01/2008-08/30/2011

Title: Protein microarrays that do not require protein spotting
Project goals: The goal of this project will be to develop a new design of protein microarrays.
Role: PI

PUBLICATIONS

1. Jedrzejak, J. **Heyduk, T**. and Kochman, M. An approach to the elucidation of the quaternary structure role in the activity of pyruvate kinase. Studies on the immobilized enzyme. *Int. J. Biochem.* **15:**695-702, 1983.

2. Dzugaj, A., **Heyduk, T**., Buczylko, J. and Kochman, M. Structural changes of rabbit liver fructose-1, 6-biphosphatase: The effect of urea and subtilisin digestion. *Arch. Biochem. Biophys*. **239**:486-490, 1985.

3. **Heyduk, T**. and Kochman, M. Temperature-induced conformational transition in rabbit muscle aldolase studied by temperature dependence of sulfhydryl reactivity. *Eur. J. Biochem*. **151:**337-343, I985.

4. **Heyduk, T**. and Kochman, M. Re-evaluation of the role of thiol groups in rabbit muscle aldolase A. *Biochim. Biophys. Acta* **874:**365-367, 1986.

5. **Heyduk, T**. Moniewska, A. and Kochman, M. The reactivity and function of cysteine residues in rabbit liver aldolase B. *Biochim. Biophys. Acta* **874:**337-346, 1986.

6. **Heyduk, T**. and Lee, J.C. *E. coli* cAMP receptor protein: Evidence for three conformational states with different promoter binding affinities. *Biochemistry* **28:**6914-6924, 1989.

7. **Heyduk, T**. and Lee, J.C. Application of fluorescence energy transfer and polarization to monitor *E. coli* cAMP receptor protein and lac promoter interaction. *Proc. Natl. Acad. Sci. USA* **87:**1744-1748, 1990.

8. **Heyduk, T**., Ryszard Michalczyk and Marian Kochman. Long-range Effects and Conformational Flexibility of Aldolase. *J. of Biol. Chem.* **266:**15650-15655. 1991.

9. Heyduk, E., **Heyduk, T**. and Lee, J.C. Global Conformational Changes in Allosteric Proteins: A Study of *E. Coli* cAMP Receptor Protein and Muscle Pyruvate Kinase. *J. of Biol. Chem.* **267:**3200-3204, 1992

10. Heyduk, E., **Heyduk, T**. and Lee, J.C. Intersubunit Communications in *E. Coli* cAMP Receptor Protein:Studies of the Ligand Binding Domain. *Biochemistry* **31:**3682-3688, 1992.

11. **Heyduk, T**. and Lee, J.C. Solution Studies on the Structure of Bent DNA in the cAMP Receptor Protein-lac DNA Complex. *Biochemistry* **31:**5165-5171, 1992

12. **Heyduk, T.**, Lee, J.C., Ebright, Y.W., Blatter, E., Zhou, Y. and Ebright, R.H. CAP-RNA polymerase interaction in solution in the absence of promoter DNA. *Nature* **364,** 548-549, 1993.

13. Heyduk, E. and **Heyduk, T**. Physical studies on intraction of transcriptional activator and RNA-polymerase: Fluorescent derivatives of CRP and RNA polymerase. *Cell Molec. Biol. Res.* **39,** 401-407, 1993.

14. Adamus, G., Arendt, A., Hargrave, P. A., **Heyduk, T**. and Palczewski, K. The Kinetics of Multi-Phosphorylation of Rhodopsin. *Archives of Biochem. Biophys.* **304:**443-447, 1993.

15. **Heyduk, T**. and Callaci, S. Fluorescence probes for studying the mechanisms of transcription activation. *SPIE Proc.* **2137:**719-724, 1994.

16. Heyduk, E. and **Heyduk, T**. Mapping protein domains involved in macromolecular interactions: A novel protein footprinting approach. *Biochemistry* **33:**9643-9650, 1994.

17. **Heyduk, T.**, Ma, Y., Tang, H. and Ebright, R.H. Fluorescence anistropy: rapid, quantitative assay for protein-DNA and protein-protein interaction. *Methods in Enzymol.* **274:**492-502, 1996

18. **Heyduk, T.**, Heyduk, E., Severinov, K., Tang, H. and Ebright, R.H. Determinants of RNA polymerase subunit for interaction with , $_1$ subunits: Hydroxyl-radical protein footprinting. *Proc. Natl. Acad. Sci. USA* **93:**10162-10166, 1996.

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22. Baichoo, N. and **Heyduk, T**. Mapping conformational changes in a protein: application of protein footprinting technique to cAMP-induced conformational changes of cAMP receptor protein (CRP). *Biochemistry* **36:** 10830-10836, 1997.

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26. Heyduk, E., and **Heyduk, T**. Probing the structure of macromolecules using microsecond time-resolved fluorescence of europium chelates. *SPIE Proc.* **3256:** 218-222, 1998.

27. Callaci, S., Heyduk, E., and **Heyduk, T**. Conformational Changes of *Escherichia coli* RNA polymerase s^{70} Factor Induced by Binding to the Core Enzyme. *J. Biol. Chem.* **273**, 329950-33001, 1998.

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31. Matlock, D. L., and **Heyduk, T.** A Real-Time Fluorescence Method to Monitor the Melting of Duplex DNA During Transcription Initiation by RNA Polymerase. *Anal. Biochem.* **247**, 140-147, 1999.

32. Baichoo, N., and **Heyduk, T.** DNA-induced conformational changes in cyclicAMP receptor protein: detection and mapping by a protein footprinting technique using multiple chemical proteases. *J. Mol. Biol.* **290,** 37-48, 1999.

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HMGI/Y family proteins and their modulation upon mitotic phosphorylation. *J. Biol. Chem*. 276, 1984-1992, 2001.

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54. Minakhin, L., Niedziela-Majka, A., Kuznedelov, K., Adelman, K., **Heyduk, T.**, and Severinov, K. Inteaction of dimeric T4 AsiA with its target sites in the RNA polymerase s^{70} subunit leads to distinct and opposite effects on transcription. *J. Mol. Biol.* **326,** 679-690, 2003.

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56. Heyduk, E., Fei, Y., and **Heyduk, T.** Homogenous fluorescence assay for cAMP. *Combinatorial Chemistry and High-throughput Screening* **6**, 183-194, 2003.

57. Simeonov, M.F., Bieber Urbauer, R.J., Gilmore, J.M., Adelman, K., Brody, E.N., Niedziela-Majka, A., Minakhin, L., **Heyduk, T.**, and Urbauer, J.L. Characterization of the interactions between the bacteriophage T4 AsiA protein and RNA polymerase. *Biochemistry* **42,** 7717-7726, 2003.

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69 Ekaterina Bogdanova, Marko Djordjevic, **Tomasz Heyduk**, and Konstantin Severinov. Transcription Regulation of the Type II Restriction-Modification System *Ahd*I. *Nucleic Acids Res.*, 36, 1429, 2008.

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Patents:

1.) U.S. Patent 6,544,746 B2 (Issued 04/08/2003), titled "A Rapid and Sensitive Proximity-based Assay for the Detection and Quantification of DNA Binding Proteins," Inventor: Tomasz Heyduk.
2.) U.S. Patent Application, Serial No: 10/062,064 (Filed 01/31/2002), titled "A Rapid and Sensitive Proximity-based Assay for the Detection and Quantification of DNA Binding Proteins," Inventor: Tomasz Heyduk.
3.) Canada Patent Application, Nationalized PCT, Serial No: not available (Filed 08/02/2002), titled "A Rapid and Sensitive Proximity-based Assay for the Detection and Quantification of DNA Binding Proteins," Inventor: Tomasz Heyduk.

4.) European Patent Application, Nationalized PCT, Serial No: 02806721.3 (Filed 03/11/2004), titled "A Rapid and Sensitive Proximity-based Assay for the Detection and Quantification of DNA Binding Proteins," Inventor: Tomasz Heyduk.
5.) China Patent Application, Nationalized PCT, Serial No: 02815825.3 (Filed 08/02/2002), titled "A Rapid and Sensitive Proximity-based Assay for the Detection and Quantification of DNA Binding Proteins," Inventor: Tomasz Heyduk.
6.) China Patent Application, Nationalized PCT, Serial No: 03803174.4 (Filing date not available), titled "A Rapid and Sensitive Assay for the Detection of Quantification of Coregulators of Nucleic Acid Binding Factors," Inventor: Tomasz Heyduk.
7.) Canada Patent Application, Nationalized PCT, Serial No: 2,473,708 (Filing date not available) titled "A Rapid and Sensitive Assay for the Detection of Quantification of Coregulators of Nucleic Acid Binding Factors," Inventor: Tomasz Heyduk.
8.) Australian Patent Application, Nationalized PCT, Serial No: 2003205320 (Filing date not available) titled "A Rapid and Sensitive Assay for the Detection of Quantification of Coregulators of Nucleic Acid Binding Factors," Inventor: Tomasz Heyduk.
9.) Japan Patent Application, Nationalized PCT, Serial No: 2003-564249 (Filing date not available), titled "A Rapid and Sensitive Assay for the Detection of Quantification of Coregulators of Nucleic Acid Binding Factors," Inventor: Tomasz Heyduk.
10.) Japan Patent Application, Nationalized PCT, Serial No: 2003-576453 (Filed 08/02/2002), titled "A Rapid and Sensitive Proximity-based Assay for the Detection and Quantification of DNA Binding Proteins," Inventor: Tomasz Heyduk.
11.) New Zealand Patent Application, Nationalized PCT, Serial No: 531020 (Filing date not available), titled "A Rapid and Sensitive Proximity-based Assay for the Detection and Quantification of DNA Binding Proteins," Inventor: Tomasz Heyduk.
12.) U.S. Provisional Patent Application, Serial No: 60/529,076 (Filed 12/12/2003), titled "Biosensors for Detecting Macromolecules and Other Analytes," Inventors: Tomasz Heyduk, Ewa Heyduk.
13.) PCT Patent Application, Serial No: PCT/US04/41315 (Filed 12/10/2004), titled "Biosensors for Detecting Macromolecules and Other Analytes," Inventors: Tomasz Heyduk, Ewa Heyduk.
14.) PCT Patent Application, Serial No: PCT/US02/24822 (Filed 08/02/2002), titled "A Rapid and Sensitive Proximity-based Assay for the Detection and Quantification of DNA Binding Proteins," Inventor: Tomasz Heyduk.
15.) PCT Patent Application, Serial No: PCT/US03/02157 (Filed 01/23/2003), titled "A Rapid and Sensitive Assay for the Detection and Quantification of Coregulators of Nucleic Acid Binding Factors," Inventor: Tomasz Heyduk.
16.) U.S. Provisional Patent Application, Serial No: Not yet assigned (Filed 6/10/05), titled "Methods for the Selection of Aptamers," Inventors: Tomasz Heyduk, Ewa Heyduk.

SUPPLEMENTAL INFORMATION:

Invited Talks and Seminars

1. Wesleyan University, Middletown, CT (1991)
2. General Meeting of American Society for Microbiology, New Orleans, LA (1992)
3. Austin Spring Meeting - "The Transcription Machine Assembly and Function" - Austin, TX(1993)
4. SPIE International Symposium - "Time-Resolved Laster Spectroscopy in Biochemistry IV" - Los Angeles, CA (1994)

5. Southern Illinois University at Carbondale (1994)
6. Wesleyan University, Middletown, CT (1994)
7. General Meeting of American Society for Microbiology, Washington, DC (1995)
8. NIH, Bethesda, MD (1995)
9. Albert Einstein College of Medicine, Bronx, NY (1995)
10. Scripps Research Institute, La Jolla, CA (1996)
11. Washington University, St. Louis, MO (1996)
12. Technical University of Wroclaw, Wroclaw, Poland (1996)
13. Southern Illinois University at Carbondale (1997)
14. Biophysical Society Meeting, New Orleans, LA (1997)
15. FASEB Summer Research Conference, Saxtons River, VT (1997)
16. Cornell University, Ithaca, NY. (1997)
17. NCI, Frederick Cancer and Development Center, Frederick, MD (1997)
18. University of Wisconsin-Madison, Madison, WI (1997)
19. Second International Assay Development for High-Throughput Screening Conference, San Diego, CA. (1998).
20. Advances in Optical Biophysics I, San Jose, CA (1998).
21. 2nd Annual Symposium on Solution Interaction of Macromolecules, Seattle, WA (1998).
22. 12th Annual Gibbs Conference on Thermodynamics (1998).
23. Sigma Chemical Co., St.Louis, MO (1999).
24. University of Goettingen, Germany (1999).
25. Oregon Health Science University, Portland, OR (2000).
26. University of Texas Medical Branch, Galveston, TX (2000).
27. 14th Annual Gibbs Conference on Thermodynamics (2000).
28. The Pennsylvania State University Medical College, Hershey, PA (2001)
29. Boston University, Boston, MA (2001).
30. Molecular Probes, Inc., Eugene, OR (2001).
31. FASEB Summer Research Conference, Saxtons River, VT (2001)
32. Biophysical Society Meeting, San Francisco, CA (2002)
33. Sigma Chemical Co., St. Louis, MO (2002)
34. Illumina, San Diego, CA (2002)
35. Rutgers University, Piscataway, NJ (2002)
36. Parnas Conference, Wroclaw, Poland (2002)
37. Loyola University, Chicago, Il (2002)
38. Louisiana State University, Baton Rouge, LA (2003)
39. Ohio State University, Columbus, OH (2003)
40. Biophotonics Meeting, San Antonio, TX (2003)
41. University of Delaware, Newark, DE (2003)
42. University of Wisconsin, Madison (2003)
43. St. Louis University, Dep. Of Chemistry (2003)
44. St. Louis University, Dep. Of Microbiology and Molecular Immunology (2004)

45. 9th FEBS Congress, Warsaw, Poland (2004)
46. University of Indiana, Bloomington, IN (2005)
47. NCI, Bethesda, MD (2005)
48. Washington University, St. Louis, MO (2006)
49. University of Indiana Medical School, Evansville, IN (2006)